Areas of Research Emphasis

Examples of specific research areas and types of characterizations appropriate for this FOA are listed below

- Molecular comparison (genomic, transcriptomic, proteomics, or metabolomic) of recurrent and non-recurrent screen-detected lesions and interval cancers,
  - to determine whether a subset of aggressive, screen-detected lesions shares features with interval cancers that likely indicate their rapidly progressing phenotypes
- Analysis of tumor heterogeneity, including topographic variation within lesions, by single cell analyses,
  - to determine whether lesions can be distinguished based on the extent of their heterogeneity in relation to immune infiltrates, matrix components, fibroblast/stromal cell features, adipose, vessels, etc.
- Phenotyping of cellular components of lesions, *including tumor cells and the microenvironment.*
  - This activity may require the development of novel panels of reagents that specifically identify distinct subsets (e.g., antibodies) and
  - methods to analyze small amounts of human tissue samples. The goal is to generate molecular signatures to detect early malignant lesions associated with increased case fatalities
- Detection of secreted factors in tumor microenvironment and/or in serum
  - specific to a subset of early lesions along with careful topographic tissue mapping to relate molecular characteristics of tumor to surrounding microenvironment or other features such as central necrosis, patterns of tissue invasion.

Areas of Research Emphasis (contd.)

- Generation of a repository of screen-detected lesions/cancers and interval cancers from existing repositories and from new, prospectively collected samples, as necessary;
  - and a data management center for the annotation and distribution of biospecimens to other components of the Consortium.
  - Prospective collection of specimens must be based on well-described and statistically justified study designs appropriate for the organ-site and type of cancer focused by the proposed research and correspondingly well-defined and accepted terms of "indolent" and "interval" lesions.
  - The collection and assembly of such repositories must also follow previously established PRoBE study design principles and guidelines (J Natl Cancer Inst. 2008 October 15; 100(20): 1432–1438).

- Leveraging knowledge based on genome-wide chromosomal instability and genome-wide association studies (GWAS) to predict progression from benign to malignant cancers.
  - Develop molecular tests based on already characterized regions of the genome that can potentially identify genes associated with risk of progression of very early lesions.

- Application of systems biology approaches and modeling using experimental data (genomics, epigenomics, proteomics, imaging, etc.) to define “disease dynamics,”
  - e.g., trajectories of each of these lesions -- growth rate, genetic and phenotypic evolution, and corresponding risk of development of clinically significant malignancy.
  - In cases where sequential imaging is possible, appropriate imaging approaches can assist in elucidating dynamic changes occurring during progressive disease and providing insights into molecular and cellular events intimately associated with lethal cancer versus non-lethal disease

Areas of Research Emphasis (contd.)

- In cases where preneoplastic specimens are not readily available, applicants can propose establishing novel mouse models, organoid cultures or patient-derived xenografts from screen-detected lesions which maintain the original architecture of the tumor in order to allow sufficient expansion for a detailed molecular analysis which could include:
  - RNA expression profiles, non-coding RNA (ncRNA), proteomics, metabolomics, cell surface markers, secreted exosomes, and DNA methylation; and
  - Analyses of both the cancer cell and cells of the microenvironment.

- With the advances made in genomic technologies using Whole Genome Sequencing (WGS) and Somatic Gene Alterations (SGA) one can develop phylogenies that infer the genomic ancestry of lesions which do or do not progress to cancer.
  - These *changes can be then modeled* to investigate disease dynamics in space and time of a "premalignant" condition, which, under selective pressures of host and environmental risk and protective factors, progresses to cancer.
  - How *the selective forces and corresponding selected genotypes shape the evolution of a cancer* during its progression to become invasive is of particular interest.

NCI-supported useful resources and collaborations (RFA, pages 5- 6)

Resources

- use existing biospecimen collections –PLCO screening trial ; NLST)
- Women's Health Initiative
- Carotene and Retinol efficiency trial

National Clinical trials Network (NCTN)

The Tumor Genome Atlas (TCGA)

Tumor Microenvironment Network (TMEN)

Urls are provided in the RFA

Review Criteria (RFA - pages 13-15)

Impact: exert a sustained, powerful influence on the research field(s) involved

Significance: Standard review criteria; in addition, specific for this FOA

- How significant is the theme of the proposed application to the understanding of the molecular and cellular factors distinguishing indolent from aggressive lesions, or screen-detected from symptom-detected interval cancers?

Investigators: Standard review criteria; in addition, specific for this FOA

- How appropriate are the *expertise and experience of the PD/PI(s)* and other researchers in the context of research on indolent versus aggressive tumor lesions and the understanding of the molecular and cellular factors distinguishing these lesions?
- Does the investigative team bring *sufficient complementary multidisciplinary scientific expertise* required for integrated and comprehensive approaches to key research problems proposed?
- Do the team members have *a relevant record of collaborations within and outside the applicant institution*? Does the team have the expertise to collect specimens, an important requirement of this FOA? Is the commitment of the PD(s)/PI(s) and other senior investigators adequate?

Review Criteria (contd.)

Innovation:

- utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach: Standard review criteria; in addition, specific for this FOA

- How adequate are plans for flexible exploitation of emerging research opportunities?
- Are the planned activities sufficiently trans-disciplinary and scientifically well integrated?
- To what degree, does the applicant team take advantage of a collaborative and interactive model of research?
- Are the structure and activities planned for the MCL adequate for the needs of the proposed studies and the anticipated trans-Consortium activities?
- How adequate are plans for prospective collection and use of specimens within the context of screen-detected and interval cancers?

Review criteria (contd.)

Environment: standard criteria; in addition, specific for this FOA

- How adequate are plans for flexible exploitation of emerging research opportunities?
- How likely is the proposed MCL to contribute unique expertise, capabilities, and/or resources to the entire Consortium?
- Does the team have the resources to collect specimens, an important requirement of this FOA?